

DIA Annual Meeting
June, 2004 – Washington DC

Update on Drug Substance and Drug Product Draft Guidances

Steve Miller, Ph.D.

Office of New Drug Chemistry (ONDC)
CDER / FDA

DIA Annual Meeting
June, 2004 – Washington

Hot Topics

 ~~Update~~ on Drug Substance and
Drug Product Draft Guidances

Steve Miller, Ph.D.

Office of New Drug Chemistry (ONDC)

CDER / FDA



Overview

- Draft Drug Product Guidance
 - P2 as opportunity for sharing your understanding of process and formulation
 - Other issues with “issues”
- Draft Drug Substance Guidance
 - Critical versus Non-Critical Process Controls
 - Reprocessing & Reworking
 - Starting Materials
 - Interim Specification / Sunset / Skip (PQIT)

Why Revise DS & DP Guidances?

- ICH CTD-Q was major influence in decision to revise the 1987 DS and DP Guidelines
- Primary purpose of revised DS and DP Guidances to provide recommendations for submitting applications formatted according to CTD-Q
 - NDAs, ANDAs, Animal Drug Applications
- Revision also provided opportunity to update 1987 guidances

Drug Product Topics

Pharmaceutical Development Report

- FDA Perspective: will help FDA to focus on aspects of manuf / control with greatest impact on quality/safety/efficacy
 - Move along the direction from “One size fits all” towards “What is critical for this product?”
 - Challenge: keep review appropriate (balance between applications)
- Industry Perspective: Mixed

Drug Product Topics

Other areas with many comments

- Manufacturing process description
 - “All process controls”
 - Critical versus non-critical process controls
- In-Process Controls (“Process Tests”)
 - Where to locate justification?
- Periodic Quality Indicator Tests (PQIT)

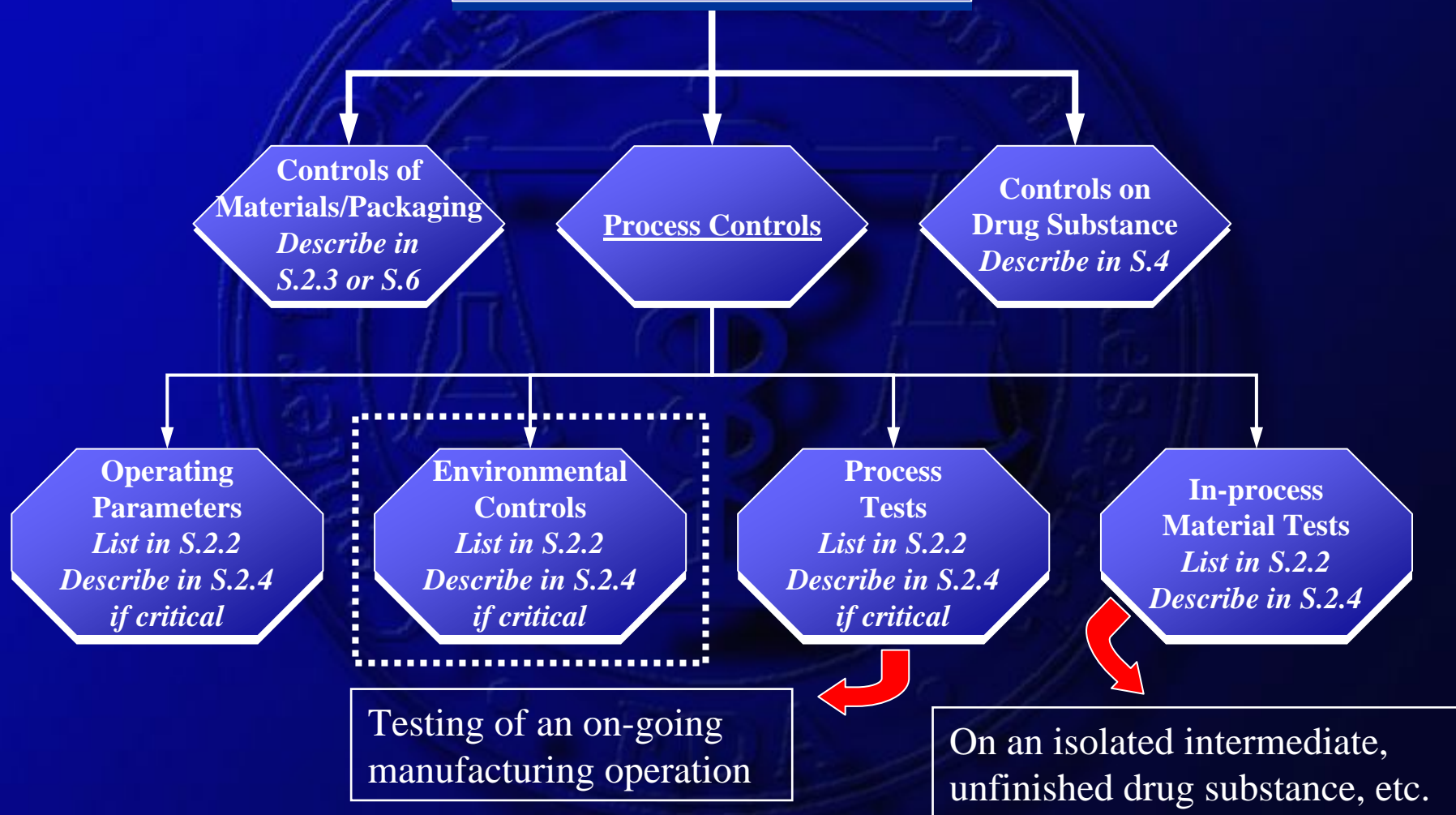
Drug Substance Topics

- Issues/Questions brought into focus by CTD-Q
 - One Issue: Critical versus Non-Critical Process Controls
- Revision also provided opportunity to assess FDA's approaches to DS issues; E.g.,
 - Reprocessing and reworking
 - Starting materials
 - Sunset / Interim Specifications / PQIT

Critical / Non-Critical Process Controls

- Critical vs. non-critical process controls
 - All Process Controls (Critical and Non-Critical)
 - S.2.2 Description of Manufacturing Process and Process Controls
 - Critical Process Controls
 - S.2.4 Controls of Critical Steps and Intermediates
 - Definition of “critical”
 - Q7A definition: a process step or process control that must be controlled within predetermined criteria to ensure that the drug substance meets its specification

Drug Substance Quality Controls



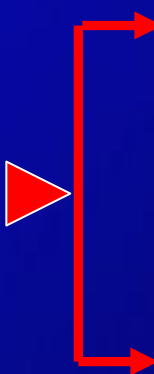
Critical / Non-Critical Process Controls

- Partitioning of information on process controls into two sections...
 - Opportunity to share knowledge of process with reviewer
 - May support customized regulatory approaches (e.g., comparability protocols)
 - Future deregulation of non-critical parameters?
 - Worth doing?
 - How to make it work?

Critical / Non-Critical Process Controls

Challenge: How to convey meaningful set of information to reviewer without restricting future optimization **Balance !**

Within an application and between apps



Expect change control with involvement of FDA reviewer (e.g., BP-1, BP-2) on appropriate operating parameters

Allow reasonable variation and optimization for non-critical parameters (record on-site under GMP)

Reprocessing & Reworking

FDA Perspective: approach in draft DS guidance is generally consistent with past practices and with ICH Q7A recommendations.

- Generally no filing for occasional reprocessing
- Occasional versus “Established”
Rework/Reprocessing

Industry Perspectives: ??

Selecting Starting Materials

- Inputs to revision of Starting Material Definition
 - 1987 DS Guidance
 - ICH Q7A API Guidance
 - “Negotiated Starting Materials”
- Today’s Hot Items
- More background in presentation from APIC-CEFIC meeting (Nov 2003)

<http://www.gmp-navigator.com/slides>

Which Compound Should be the Starting Material?

- General criteria/approach would be valuable
 - uniform approach across appls, NDA/ANDA
 - currently: much interest and effort; case-by-case
- Three main considerations:
 - how much of the synthesis to “report?”
 - how complex can the SM be?
 - what specification is appropriate for the SM?

Definition of SM Beginning with the 1987 DS Guideline

“What constitutes the "starting material" may not always be obvious.”

“Generally the decision about what is the starting material has been reached by agreement between the applicant and the FDA chemist before submission of the NDA (e.g., during an IND End-of Phase 2 meeting, or pre-NDA meeting).”



Definition of SM in ICH Q7A

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Definition of SM in ICH Q7A (cont'd)

- More an inclusive statement
 - Defines what *may* be a SM
 - Not how to select the SM(s) for a synthesis from the raw materials, intermediates, etc.
- Main purpose may be to clarify that GMPs start with the use of the SM whether purchased or made in-house
- Supports determination of SM as part of application review process

Recommended Approach to Starting Materials in Draft DS Guidance

- Selection Criteria
 - Carryover of impurities into DS
 - Propinquity (# of steps) 
 - Isolated and purified substances
 - Complexity of Structure
 - Exception for chemicals with significant non-pharmaceutical markets 
 - Robust SM Specification for Minimally Insulating Syntheses
- Properties of Synthesis
- Properties of SM

Hypothetical Synthesis



- Starting material for each branch
- Each reaction arrow represents a change in structure (not just salt change)
- J can be a starting material, too!

Applicant's Tendency

reduce costly GMP manufacture

reduce reporting of process variation/optimization

increase flexibility of process and sourcing

====> move SM forward ==>



<==== keep more steps under BACPAC =====

Agency's Tendency

control impurities (from SM; from subsequent steps)

ensure identity of drug substance



← keep more steps under BACPAC →

WHY?

FDA/Firm Responsibility to Evaluate DS Controls
Are they sufficient to ensure safety of DS?

What solvents/reagents are used? Controls needed?
Process Controls as well as DS Specification

What related substances are carried into DS?
Now; and for new sources of SM in future

Balancing: **Firm** \rightleftharpoons **FDA**



Purification Processes in Reported Synthesis = ‘Insulator’ for DS

Future sources of SM (new routes) may bring new related substances

Multiple (different) purification steps more likely to purge them out

Synthesis Reported in Application is under BACPAC-1 Control

Assessing the Reported Portion of the Synthesis

Will it be a good “Insulator?”

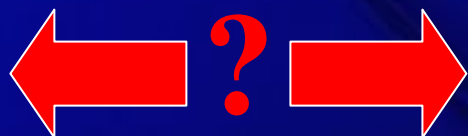
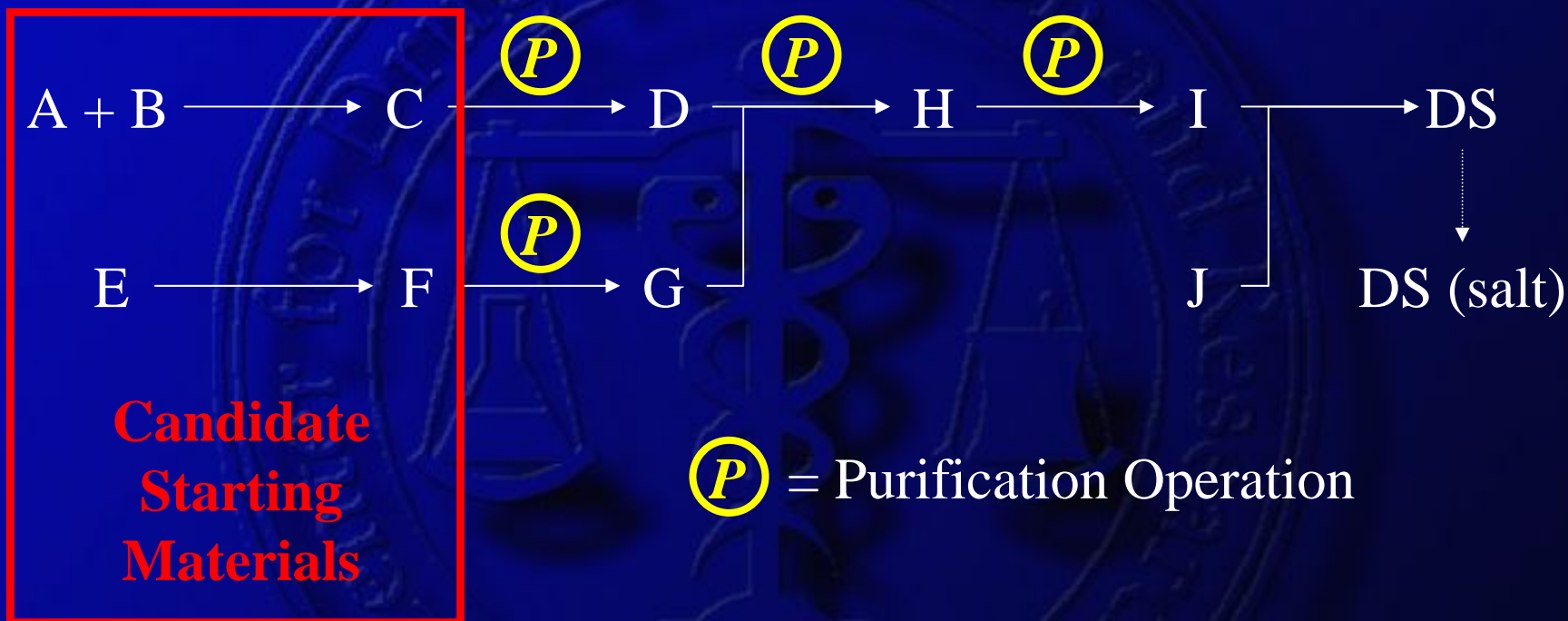
Are there a reasonable number of purification steps?

- What is a reasonable number? Counting from SM or FI?
- Count all purifications equally? Crystallization vs extractive work-up vs solvent evaporation
- Keep a reasonable amount of final synthetic steps under BP-1 change control (solvents, reagents, process controls)

“Propinquity” (proximity; nearness)

A starting material should be separated from the final intermediate by several reaction steps that result in isolated and purified intermediates.

Propinquity Selection Principle

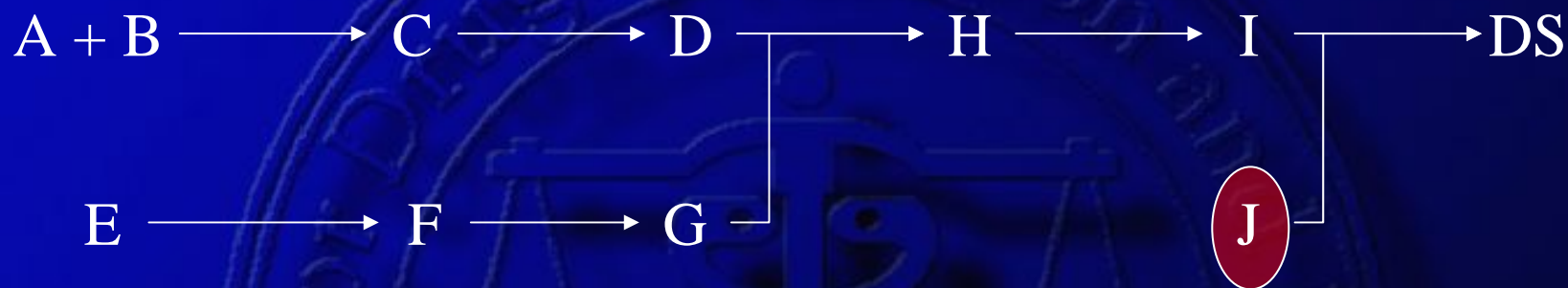


Propinquity in Jan 04 draft:
several reaction steps with
purifications



How to Handle Commercially Available Chemicals?

A Commercial Chemical Could be Used Late in the Synthesis

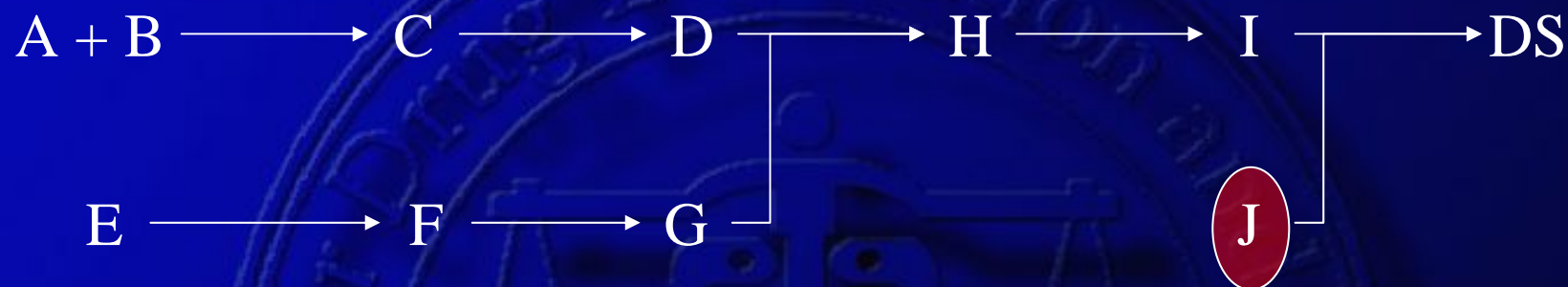


Pros and Cons of Defining J as a Starting Material:

- (-) Little synthetic “insulation” between J and DS
- (+) Probably not overly complex
- (-) Synthesis of J generally cannot be controlled by applicant
- (+) Applicant can purify J if needed

Overly burdensome to require synthesis of J under GMPs
(J fits with the spirit of commercially avail 1987 DS Guide)

What To Do with Commercial Chemicals Such as J?



J unlikely to fit all selection principles

Carry over of impurities to DS ?

—Propinquity—

Isolated and purified substance

Complexity of structure

Draft DS Guidance recommends exempting J from the selection principles because it ~~is commercially available~~

“has a Significant Non-Pharmaceutical Market”

~~Commercially Available Chemicals~~

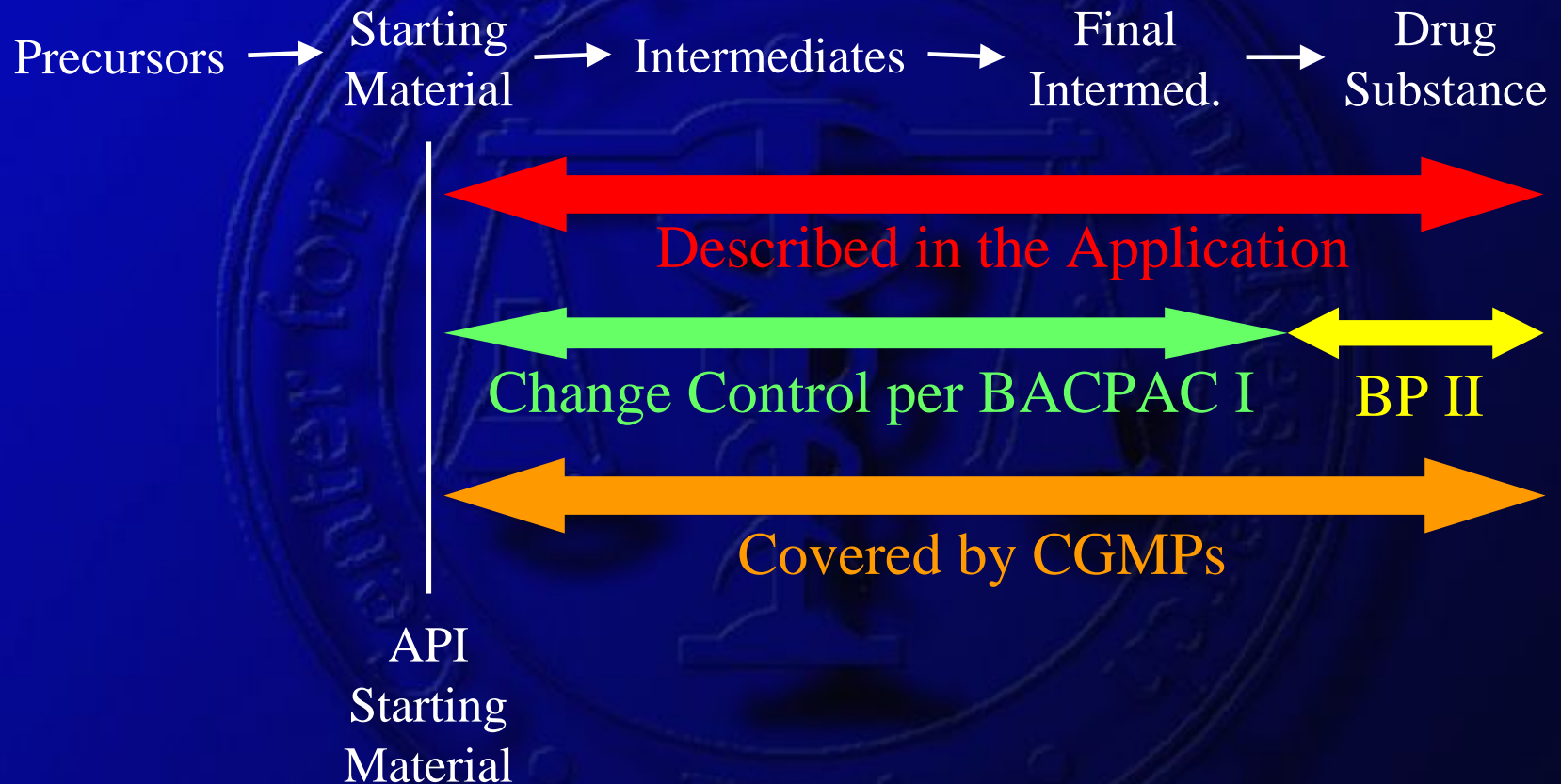
Chemicals with Non-Pharmaceutical Market

- A significant non-pharmaceutical market can be considered to exist...
 - if the quantity of the chemical needed for the production of the drug substance represents only a small fraction of the chemical's total market
 - regardless of whether the chemical is made by the drug substance manufacturer for its own use or is obtained from another firm

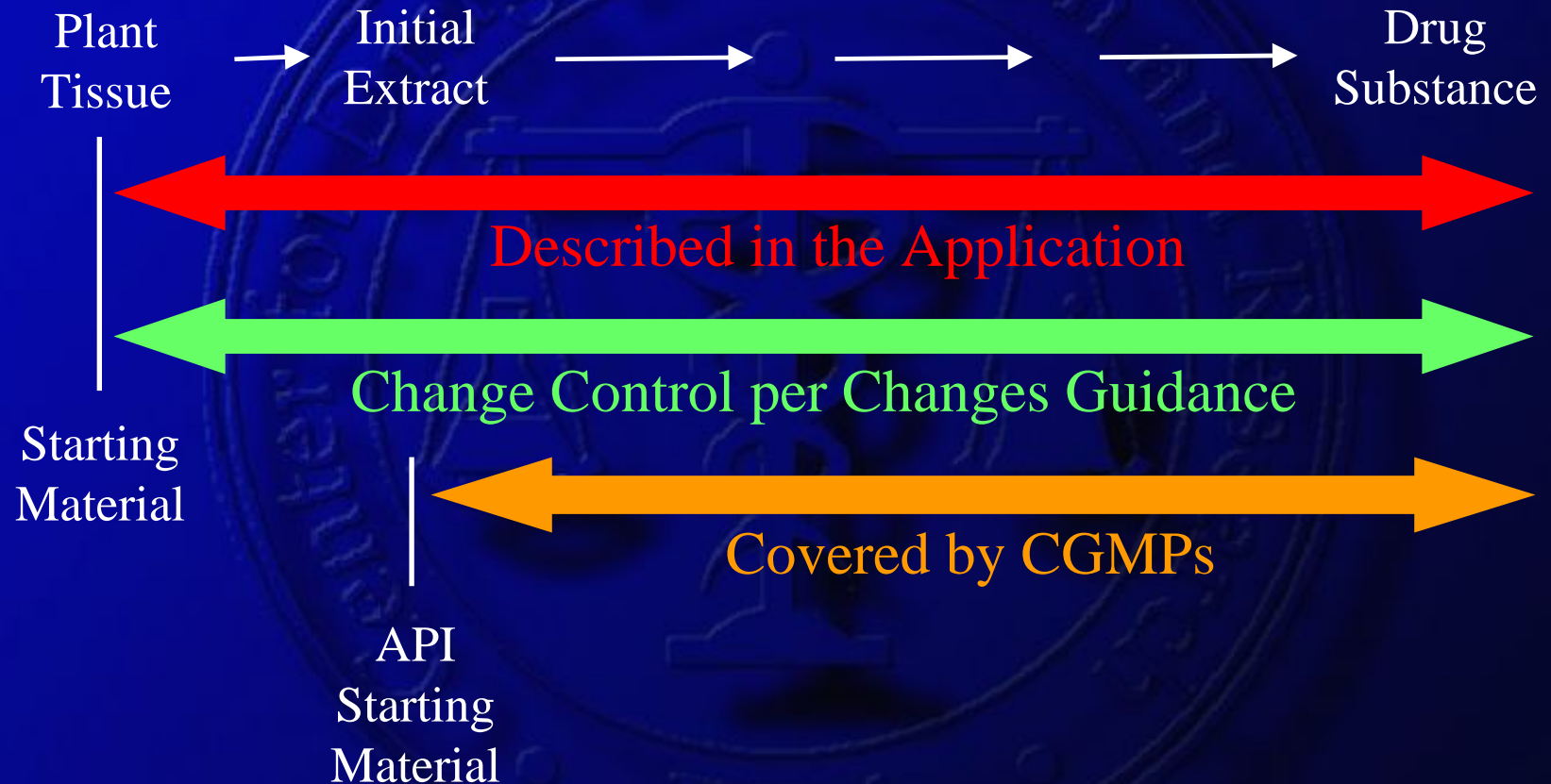
Starting Materials and API Starting Materials

- In general, the starting material and API starting material should be the same for a synthetic drug substance
- However for a drug substance derived from a biological source, the starting material (e.g., plant) and API starting material (e.g., extract) can be different

Synthetic Starting Materials



Starting Materials from *Plants* or *Animals*



Sunset / Interim Specifications

Periodic Quality Indicator Tests (PQIT)

FDA Perspective: These provide flexibility for situations where:

- a) It is not clear whether routine testing of an attribute is needed to maintain quality/safety/efficacy – agree on limited testing of commercial batches, then decide
- b) Routine testing for batch release is appropriate, but acceptance criteria difficult to agree on without more data

Industry Perspectives: Seemed strongly favorable at AAPS/FDA Workshop on DS/DP Specs – how about now?

Acknowledgement

Members of the Drug Product Technical Committee

CDER

Upinder S. Atwal

Norman R. Schmuff

Vispi P. Bhavnagri

Ruth M. Ganunis

Nallaperum Chidambaram

Lawrence Yu

Marie Kowblansky

Rashmi Patel

CBER Associate

Chris Joneckis

Compliance Associate

Albinus M. D'Sa

Acknowledgement

Members of the Drug Substance Technical Committee

CDER

John Smith

Bing Cai

Eric Duffy

Charles Hoiberg

Ramsharan Mittal

Tom Oliver

Anil Pendse

Suong Tran

Scott Furness

Jon Clark

Yung-Ao Hsieh

Robbe Lyon

Stephen Moore

Larry Ouderkirk

Edwin Ramos

Naiqi Ya

CVM

Dennis Bensley

Raafat Fahmy

CBER Associate

Chris Joneckis

Compliance Associate

Edwin Rivera



Thank You

MillerS@cder.fda.gov

Type of Manufacturing	Application of this guidance to steps (shown in gray) used in this type of manufacturing				
Chemical Manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



Other Talks of Interest

Talks on reasoning behind the revision of the DS Guidance from previous chair of DSTC (John Smith)

<http://www.fda.gov/cder/ondc/Presentations/Presentations.htm>

Presentation by Wendy Mavroudakakis and Betsy Fritschel including thoughts on starting material selection (prior to release of CDER draft DS guide)

<http://www.gmp-navigator.com/slides>